APPENDIX A:

140 (New): A modified pyrrhocoricin peptide of the formula R^1 -SEQ ID NO: 1- R^2 having anti-bacterial activity,

wherein SEQ ID NO: 1 is -Asp-Lys-Gly-Ser-Tyr-Leu-Pro-Arg-Pro-Thr-Pro-Pro-Arg-Pro-Ile-Tyr-Asn-Arg- ,

wherein said Thr in SEQ ID NO: 1 lacks the glycosylation of the Thr residue of naturally-occurring pyrrhocoricin;

wherein said Ser-Tyr amino acids and said Asn-Arg amino acids in said SEQ ID NO: 1 are independently selected from the group consisting of naturally-occurring amino acids and unnatural amino acids that improve the stability of the bond between the Ser-Tyr or Asn-Arg amino acids against protease degradation;

wherein R^1 adds a net positive charge to the N-terminus of said peptide and is selected from the group consisting of

(a) a straight chain, branched, cyclic or heterocyclic alkyl group;

(b) a straight chain, branched, cyclic or heterocyclic alkanoyl group;

(c) a positively charged reporter group; and

(d) a sequence consisting of between 1 to 15 additional amino acids, wherein said additional amino acids are optionally substituted by one or more of (a), (b), or (c); and wherein said additional amino acids are capable of cyclizing the peptide by bridging between the N- and C-termini thereof; and

wherein R^2 is selected from the group consisting of

(e) a free hydroxyl, an amide, an imide, or a sugar;

(f) a sequence consisting of 1 to 15 additional amino acids, wherein said additional amino acids are optionally substituted by a free hydroxyl, an amide, an imide, or a sugar; and wherein said additional amino acids optionally cyclize the peptide by bridging between the N- and C- termini thereof.

141 (New): The peptide according to claim 140 wherein said additional amino acids of (d), and (f) are independently selected from naturally-occurring or unnatural amino acids.

142 (New): The peptide according to claim 141, wherein said unnatural amino acids are selected from the group consisting of a D-amino acid, a diaminocarboxylic acid, an amide of a diaminocarboxylic amide group and an amino cycloalkane carboxylic acid.

90 (Currently Amended). The peptide according to claim 141, wherein an additional amino acids of (d) or (f) is an unnatural amino acid substituted with a modifying sugars or imide.

105 (Currently Amended). The peptide according to claim 142, wherein at least one amino acid is a D amino acid.

91 (Currently Amended). The peptide according to claim 140, wherein said R^1 (d) is selected from the group consisting of D-Val-, Arg-Val-, Lys-Val-, and Lys-Val-Asp-Lys-Val- SEQ ID NO: 5.

92 (Currently Amended). The peptide according to claim 140, wherein said R^1 (d) is selected from the group consisting of Acetyl-Arg-Val-; Acetyl-Lys-Val-; and Acetyl-Lys-Val-Asp-Lys-Val- SEQ ID NO: 29.

93 (Currently Amended). The peptide according to claim 140, wherein said R^1 (c) is biotin.

94 (Currently Amended). The peptide according to claim 140, wherein said R^1 (c) is 5(6) carboxyfluorescein.

95 (Currently Amended). The peptide according to claim 140, wherein R^1 (c) is radioactive.

143 (New): The peptide according to claim 140, wherein R^1 (d) is a sequence consisting of between 1 to 15 additional amino acids, which comprises a portion of SEQ ID NO: 1.

144 (New): The peptide according to claim 132, wherein R^1 (d) comprises -Arg-Pro-Pro-Thr-Pro-Arg-Pro-Leu-Lys-Val- SEQ ID NO: 3.

96 (Currently Amended). The peptide according to claim 144, wherein R^1 (d) is capable of bridging between the N- terminus and C- terminus of said peptide.

97 (Currently Amended). The peptide according to claim 96, wherein R^1 (d) is -Arg-Pro-Pro-Thr-Pro-Arg-Pro-Leu-Lys-Val- SEQ ID NO: 3, wherein said Val is linked to the N-terminal Asp of SEQ ID NO: 1 and the N-terminal amino acid of R^1 is linked by a covalent bond to the C-terminal amino acid of R^2.

145 (New): The peptide according to claim 140, wherein R^1 (a) is 1-aminocycloalkane carboxylic acid.

98 (Currently Amended). The peptide according to claim 145, wherein said R^1 (a) is 1-aminocyclohexane carboxylic acid.

146 (New): The peptide according to claim 140, wherein R^1 (a) is a cyclic or heterocyclic alkyl or alkanoyl group.

147 (New): The peptide according to claim 146, wherein R^1 (a) is an N-amino-N-carboxy cyclic alkyl or alkanoyl group.

99 (Currently Amended). The peptide according to claim 140, wherein said R^1 provides a detectable signal, optionally upon interaction with other compounds.

100 (Currently Amended). The peptide according to claim 140, wherein R^2 (e) is the amide of β-acetyl-2,3-diamino propionic acid.

103 (Currently Amended). The peptide according to claim 140, wherein R^2 (f) is selected from the group consisting of D-Asn, L-Asn, Asp, and Asn-R^3, wherein R^3 is a sugar.

104 (Previously Presented). The peptide according to claim 103, wherein R^3 is selected from the group consisting of 2-acetamido-2-deoxyglucose and triacetyl 2-acetamido-2-deoxyglucose.

101 (Currently Amended). The peptide according to claim 144, wherein R^2 (f) is a sequence of 1 to 15 additional amino acids capable of cyclizing the modified peptide by bridging between the N- and C- termini of said peptide.

148 (New): The peptide according to claim 140, wherein R^1(f) is a sequence consisting of between 1 to 15 additional amino acids, which comprises a portion of SEQ ID NO: 1.

149 (New): The peptide according to claim 148, wherein said portion of SEQ ID NO: 1 is in C-terminal to N-terminal order.

150 (New): The peptide according to claim 149, wherein said portion is -Arg-Pro-Pro-Thr-Pro-Arg-Pro-Leu-Lys-Val- SEQ ID NO: 3.

151 (New): The peptide according to claim 101, wherein an additional amino acid of R^2 (f) is an unnatural amino acid.

152 (New): The peptide according to claim 148, wherein an additional amino acid of R^2 (f) is an unnatural amino acid.

153 (New): The peptide according to claim 151, wherein said unnatural amino acid is a diaminocarboxylic acid or an amide of a diaminocarboxylic acid.

154 (New): The peptide according to claim 152 wherein said unnatural amino acid is a diaminocarboxylic acid or an amide of a diaminocarboxylic acid.

155 (New): The peptide according to claim 140, wherein said R^2 (f) is a sequence consisting of from 1 to 15 additional amino acids, wherein said additional amino acids are selected from the group consisting of an Asn, a diaminocarboxylic acid, an amide of a diaminocarboxylic acid, a sequence of amino acids that duplicate at least a portion of SEQ ID NO: 1, and combinations thereof.

106 (Currently Amended). The peptide according to claim 140, which is non-glycosylated.

107 (Currently Amended). The peptide according to claim 140, which is a cyclic peptide in which R^1, R^2, or a combination of R^1 and R^2 form an amino acid sequence of up to 15 amino acids in length capable of bridging the N- and C- termini of said peptide.

108 (Currently Amended). The peptide according to claim 107, wherein said sequence duplicates at least a portion of SEQ ID NO: 1.

109 (Currently Amended). The peptide according to claim 140, wherein at least one conventional amide bond between two amino acids in said sequence is replaced with a non-cleavable bond.

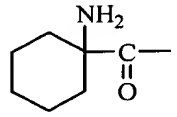
110 (Previously Presented). The peptide according to claim 109, wherein said non-cleavable bond is a thio-amide bond or a reduced amide bond.

120 (Currently Amended). The peptide according to claim ~~1~~ 140, wherein R^1 is Acetyl-Lys-Val-Asp-Lys-Val- SEQ ID NO: 29, and R^2 is Asn.

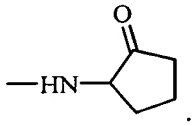
121 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Arg-Val, and R^2 is Asn.

122 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Lys-Val, and R^2 is Asn.

123 (Currently Amended). The peptide according to claim 140, wherein

R1 is  , and R^2 is Asn.

124 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Lys-Val, and

R2 is  .

125 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Lys-Val, and R^2 is NH-CH-$CONH_2$

CH_2-NH-$COCH_3$.

126 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Lys-Val, and R^2 is Asn-2-acetamido-2-deoxyglucose.

127 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Lys-Val, and R^2 is Asn-triacetyl-2-acetamido-2-deoxyglucose.

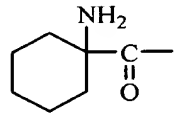
128 (Currently Amended). The peptide according to claim 140, wherein R^1 is D-Val, and R^2 is D-Asn.

129 (Currently Amended). The peptide according to claim 140, wherein R^1 is Biotin-Lys-Val, and R^2 is Asn.

130 (Currently Amended). The peptide according to claim 140, wherein R^1 is 5(6)-carboxyfluorescein-Lys-Val, and R^2 is Asn.

131 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Lys-Val, and R^2 is Asp.

132 (Currently Amended). The peptide according to claim 140, wherein

R1 is  , and

R^2 is NH-CH-$CONH_2$
|
CH_2-NH-$COCH_3$.

133 (Currently Amended). The peptide according to claim 140, wherein R^1 is Acetyl-Arg-Val, and R^2 is NH-CH-$CONH_2$
|
CH_2-NH-$COCH_3$.

134 (Currently Amended). The peptide according to claim 140, wherein R^1 is Val, and R^2 is NH-CH-$CONH_2$
|
CH_2-NH-$COCH_3$.

135 (Previously Presented). The peptide according to claim 107, wherein R^1 is Val, and R^2 is Asn-Arg-Pro-Pro-Thr-Pro-Arg-Pro-Leu-Lys-, wherein the Lys group of R^2 is bound to Val of R^1.

156 (New): The peptide according to claim 140, wherein said Ser-Tyr amino acids in SEQ ID NO: 1 are linked by a protected amide bond.

157 (New): The peptide according to claim 156 wherein said protected amide bond is selected from the group consisting of a reduced amide bond and a thioamide bond.

158 (New): The peptide according to claim 140, wherein said Asn-Arg amino acids in SEQ ID NO: 1 are linked by a protected amide bond.

159 (New): The peptide according to claim 158, wherein said protected amide bond is selected from the group consisting of a reduced amide bond, and a thioamide bond.

87 (Currently Amended). The peptide according to claim 140, which is fused to a protein.

160 (New): A multivalent composition having anti-bacterial activity and comprising at least two modified pyrrhocoricin peptides, each peptide having the formula R^1 -SEQ ID NO: 1- R^2,

wherein SEQ ID NO: 1 is -Asp-Lys-Gly-Ser-Tyr-Leu-Pro-Arg-Pro-Thr-Pro-Pro-Arg-Pro-Ile-Tyr-Asn-Arg- ,

wherein said Thr in SEQ ID NO: 1 lacks the glycosylation of the Thr residue of naturally-occurring pyrrhocoricin;

wherein said Ser-Tyr amino acids and said Asn-Arg amino acids in said SEQ ID NO: 1 are independently selected from the group consisting of naturally-occurring amino

acids and unnatural amino acids that improve the stability of the bond between the Ser-Tyr or Asn-Arg amino acids against protease degradation;

wherein R^1 adds a net positive charge to the N-terminus of said peptide and is selected from the group consisting of

(a) a straight chain, branched, cyclic or heterocyclic alkyl group;

(b) a straight chain, branched, cyclic or heterocyclic alkanoyl group;

(c) a positively charged reporter group; and

(d) a sequence consisting of between 1 to 15 additional amino acids, wherein said additional amino acids are optionally substituted by one or more of (a), (b), or (c); and wherein said additional amino acids are capable of cyclizing the peptide by bridging between the N- and C-termini thereof; and

wherein R^2 is selected from the group consisting of

(e) a free hydroxyl, an amide, an imide, or a sugar;

(f) a sequence consisting of 1 to 15 additional amino acids, wherein said additional amino acids are optionally substituted by a free hydroxyl, an amide, an imide, or a sugar; and wherein said additional amino acids are capable of cyclizing the peptide by bridging between the termini thereof.

161 (New): The composition according to claim 160, wherein said Ser-Tyr amino acids in SEQ ID NO: 1 are linked by a protected amide bond.

162 (New): The composition according to claim 161, wherein said protected amide bond is selected from the group consisting of a reduced amide bond and a thioamide bond.

163 (New): The composition according to claim 160, wherein said Asn-Arg amino acids in SEQ ID NO: 1 are linked by a protected amide bond.

164 (New): The composition according to claim 163, wherein said protected amide bond is selected from the group consisting of a reduced amide bond and a thioamide bond.

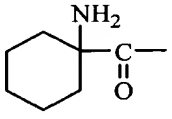
165 (New): The composition according to claim 160, wherein said additional amino acids of (d), and (f) are independently selected from naturally-occurring or unnatural amino acids.

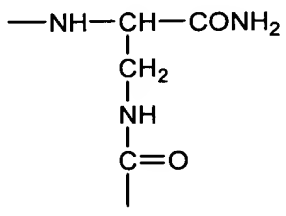
166 (New): The composition according to claim 161, wherein said unnatural amino acids are selected from the group consisting of a D-amino acid, a diaminocarboxylic acid, an amide of a diaminocarboxylic amide group and an amino cyclohexane carboxylic acid.

74 (Currently Amended). The composition according to claim 160, which is a dimer comprising two independently modified peptides, wherein the R^2 of one said modified peptide is attached to the R^2 of the other said modified peptide.

114 (Currently Amended). The composition according to claim 160, which is a dimer comprising two independently modified peptides, wherein one modified peptide is covalently linked to the R^2 of another modified peptide.

137 (Currently Amended). The composition according to claim 74, comprising two said modified peptides linked at their R^2 groups, wherein:

each R1 is  ,

the R2 of one said modified peptide is  ,

and the R^2 of the other said modified peptide is $-CH\text{-}CH_2\text{-}NH\text{-}COCH_3$.

84 (Currently Amended). The composition according to claim 114, wherein R^2 of one said modified peptide is an alkanoic acid group and wherein another said modified peptide is linked to the same R^2.

118 (Currently Amended). The composition according to claim 114, wherein said R^2 of one of said independently modified peptides comprises the amide of β-acetyl-2,3-diamino propionic acid and wherein an additional modified peptide is linked to said amide at its carboxyl terminus.

76 (Currently Amended). The composition according to claim 160, comprising at least two said independently modified peptides wherein one said modified peptides is attached to a branched construct of another said modified peptides in the composition.

113 (Currently Amended). The composition according to claim 143, comprising at least two said independently modified peptides, wherein at least one or more of said modified peptides is attached to a carrier.

119 (Currently Amended). The composition according to claim 160, further comprising an amino acid or chemical compound at the amino or carboxy termini of said modified peptides to link two or more said modified peptides together.

167 (New): The composition according to claim 160, wherein R^1 (d) is capable of bridging between the free termini of said peptides.

168 (New): The composition according to claim 160, wherein said R^1 (a) comprises a cyclic alkyl group.

169 (New): The composition according to claim 160, wherein said R^1 (a) comprises a 1-aminocycloalkane carboxylic acid.

170 (New): The composition according to claim 169, wherein said R^1 (a) comprises a 1-aminocyclohexane carboxylic acid.

171 (New): The peptide according to claim 160, wherein R^1 (a) is a cyclic or heterocyclic alkyl or alkanoyl group.

172 (New): The peptide according to claim 171, wherein R^1 (a) is an N-amino-N-carboxy cyclic alkyl or alkanoyl group.

173 (New): The composition according to claim 160, wherein R^2 (f) is a sequence of 1 to 15 additional amino acids capable of cyclizing the peptides by bridging between the free termini of said peptides.

174 (New): The composition according to claim 160, wherein an additional amino acid of R^2 (f) is an unnatural amino acid.

175 (New): The composition according to claim 174, wherein said unnatural amino acid is a diaminocarboxylic acid or an amide of a diaminocarboxylic acid.

176 (New): The composition according to claim 160, wherein said R^2 (f) is a sequence consisting of from 1 to 15 additional amino acids, wherein said additional amino acids are selected from the group consisting of an Asn, a diaminocarboxylic acid, an amide of a diaminocarboxylic acid, a sequence of amino acids that duplicate at least a portion of SEQ ID NO: 1, and combinations thereof.

177 (New): The composition according to claim 160, wherein said R^2 (f) is a sequence consisting of from 1 to 15 additional amino acids, wherein said additional amino acids are selected from the group consisting of an Asn, a diaminopropanecarboxylic acid, an amide of a diaminopropane carboxylic acid, a sequence of amino acids that duplicate at least a portion of SEQ ID NO: 1, and combinations thereof.

178 (New): The composition according to claim 160, which is non-glycosylated.

179 (New): The composition according to claim 160, wherein at least one conventional amide bond between two amino acids in said sequence is replaced with a non-cleavable bond.

180 (New): The composition according to claim 179, wherein said non-cleavable bond is a protected amide bond.

115 (Currently Amended). The composition according to claim 160, which comprises a multiple antigenic peptide.

181 (New): The composition according to claim 160, which comprises multiple copies of said modified peptide linked by attachment to one or more linked diaminocarboxylic acid groups.

182 (New): The composition according to claim 181, wherein said diaminoacarboxylic acid group is a lysine.

183 (New): The composition according to claim 182, wherein said diaminoacarboxylic acid group is further linked to a β-alanine substituent.

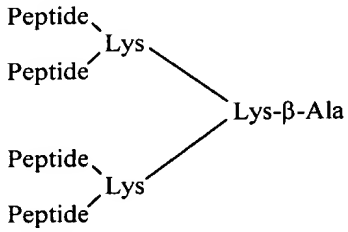
116 (Previously Presented). The composition according to claim 115, wherein said multiple antigenic peptide comprises a β-alanine substituent on a poly-lysine core.

184 (New): The composition according to claim 115, comprising a dimer of two modified peptides.

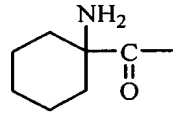
185 (New): The composition according to claim 115, comprising three modified peptides.

117 (Currently Amended). The composition according to claim 115, comprising at least four peptides.

136 (Currently Amended). The composition according to claim 117, comprising the structure



wherein each said peptide is of the formula R^1 SEQ ID NO: 1 – R^2, wherein:

R1 is 

,and R^2 is Asn.

138 (Currently Amended). The composition according to claim 136, wherein said multiple antigenic peptide is produced synthetically or recombinantly.

139 (Currently Amended). The composition according to claim 136, wherein one or more of said modified peptides is a synthetic peptide fused to a peptide sequence, protein or chemical compound that enhances the bioavailability of said modified peptides.

79 (Currently Amended). A method of treating a mammalian infection comprising administering to a mammal having said infection an amount of a peptide of claim 140.

186 (New): A method of treating a mammalian infection comprising administering to a mammal having said infection an amount of a composition of claim 160.

81 (Currently Amended and Withdrawn). A method for identifying pharmaceutical compounds comprising:

(i) performing a competitive assay with:

(a) a microorganism susceptible to a peptide of claim 140;

(b) a peptide of claim 140; and

(c) at least one test compound;

(ii) exposing (a) to (b) and (c); and

(iii) identifying said test compound which competitively displaces the binding of said peptide to a receptor on said microorganism.

82 (Currently Amended). A pharmaceutical composition comprising one or more of the peptides of claim 140 in a pharmaceutically acceptable carrier.

83 (Currently Amended). A pharmaceutical composition comprising one or more of the compositions of claim 160 in a pharmaceutically acceptable carrier.